**REMARKS**

1. We thank the examiner for allowing claims 40-43, 107, 109-110, 120-138, 140-149, 158-161. (OA §11).

2. Claim 150 (OA §§8, 10)

2.1. The Examiner says that there is no basis for combining the limitations of (1) 80% identity with the whole GH, and (2) 80% identity within the third alpha helix.

The language on which we relied is at page 18, lines 6-12:

> Preferably, the polypeptide is a least about 50% homologous, more preferably at least 80% homologous, with bGH or hGH in the subsequence substantially corresponding to the third alpha helix (approximately, residues 106-129) of bGH, and more preferably over the entire length of the polypeptide (ignoring extraneous non-bGH-related fusions to the amino-terminus or carboxy-terminus).

The "more preferably" language seems to be at least consistent with the teaching of the combination.

Consider also page 17, lines 16-30:

> The present invention is not limited to the mutation of the third alpha helix of bGH or bGH. Rather, it encompasses the mutation of the third alpha helix of any mammalian or other vertebrate GH, including, but not limited to, the GHs whose sequences are given in Watahiki (1989): flounder, yellowtail, tuna, salmon, chicken, rat, porcine, ovine, bovine and human GHs. Expression of mutants of other GHs is facilitated by the availability of genes encoding the latter. See, e.g., Goeddel et al., Nature 281:544-548 (1979). In addition, the present invention is not limited to muteins of mammalian or vertebrate GHs comprising

> mutations only within the third alpha helix, but also encompasses muteins having mutations outside the third alpha helix in addition to those mutations within the third alpha helix such that the muteins exhibit GH antagonist activity.

If the mutein had mutations "only within the third alpha helix", it would satisfy both limitations (1) and (2). Thus, the combination is contemplated.

See also page 24, lines 1-5:

> In addition to any mutations in the third alpha helix that are deemed necessary to impart the desired growth-inhibitory activity, additional mutations are possible outside of the third alpha helix that will leave the growth-inhibitory activity or other antagonist activity intact.

2.2. The Examiner also raises some definiteness issues with this claim.

2.3. We think it clear from the discussion in 2.1 that two separate calculations are contemplated by claim 150 (vs. helix 3 and vs. whole protein). Note further that at p. 14, lines 19-24, both overall and helix-3 only % identities are set forth.

2.4. With regard to defining the bounds of helix 3, the Examiner cites page 18, line 9 ("approximately, residues 106-129"). Page 14, line 22 refers to it as "bGH 109-126". Page 18, lines 23-25 say that it was "reported" as "108-127", "defined" as 106-129, and has a "central region (109-126)" with greater secondary structure.

We believe the formal definition (AAs 106-129) at page 15, lines 23-24 controls. To expedite prosecution, we have amended claim 150 accordingly.

2.5. We do not identify the modified helix as the helix

3 of the variant since mutations could create or eliminate earlier helices. We have inserted "corresponding to the third alpha helix of bovine growth hormone", after "has an alpha helix". In the case of hGH, we believe these corresponding AAs would be 107-130. Note that "corresponding" means "properly aligned with and similar to", not "identical to".

2.6. It is excessively formalistic to require antecedent basis for the "third alpha helix" of bGH. It is an inherent feature of bGH.

3. Claims 32 and 38 (OA §10, P5)

These claims formerly depended from cancelled claims 29 and 11, respectively. Their dependencies have been shifted to claim 139. In addition, they have been amended to conform stylistically with the other claims (e.g., "native" instead of "first").

4. Claims 159 and 160 (OA §10, P6)

These claims are worded in terms of volume instead of molecular weight in view of the "cleft theory stated at page 20, lines 9-21. The term "bulkier" clearly refers to volume. Note also page 21 lines 6-10 and 34 ("bulk"), and the tabulation of volumes at page 23. Hence, claims 159 and 160 are proper.

If preferred by the Examiner, we are certainly willing to replace the present limitations of 159 and 160 with a list of AAs based on page 23, i.e.

159 Pro, Glu, Val, Gln, His, Met, Ile, Leu, Lys, Arg, Phe, Tyr, Trp

160 Leu, Lys, Arg, Phe, Tyr, Trp.

5. Claim 162 (OA §10, p. 6)

This claim has been made dependent on claim 161.

6. Claim 139 (OA §6)

We do not believe that it is safe to assume that "there is only a single factor in each species which is considered growth hormone". See, e.g., WO91/008701 (Ref. AJ, October 10, 1995 IDS) (Upjohn), indicating that there at least six major forms of bovine GH.

Respectfully submitted,

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